medicines
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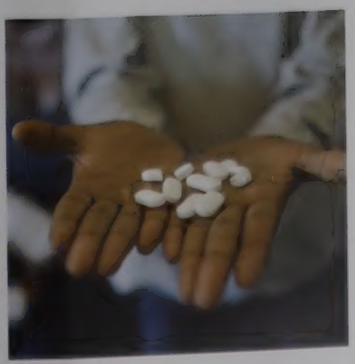
ARV PRIORITY LIST FOR THE MEDICINES PATENT POOL

Working paper: September 2011



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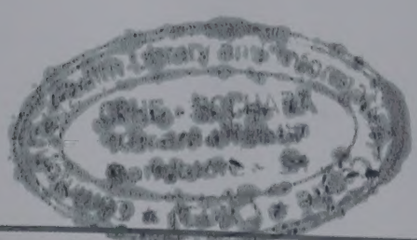
Acronyms & Definitions

Acronym	
AIDS	Acquired Immune Deficiency Syndrome
ARIPO	African Regional Intellectual Property Organization
ART	Antiretroviral treatment
ARV	Antiretroviral drug
EAPO	Eurasian Patent Organization
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
FDC	Fixed Dose Combination
HIV	Human Immunodeficiency Virus
IP	Intellectual Property
LDC	Least Developed Countries
LIC	Low Income Countries
MIC	Middle Income Countries
NIH	United States National Institutes of Health
NNRTI	Non Nucleoside Reverse Transcriptase Inhibitor
OAPI	Organisation Africaine de la Proprieté Intellectuelle/African Organization of Industrial Property
PMTCT	Prevention of Mother to Child Transmission of HIV
SSA	Sub-Saharan Africa
WHO	World Health Organization
WIPO	World Intellectual Property Organization

Antiretroviral Medicines	
3TC	Lamivudine
ABC	Abacavir
ATV	Atazanavir
AZT	Zidovudine
COB	Cobicistat
d4T	Stavudine
ddI	Didanosine
DLG	Dolutegravir
DRV	Darunavir
EFV	Efavirenz
ETR	Etravirine
EVG	Elvitegravir
FOS	Fosamprenavir
FTC	Emtricitabine
IDV	Indinavir

LPV	Lopinavir
NVP	Nevirapine
RAL	Raltegravir
RIL	Rilpivirine
RTV	Ritonavir
r	Ritonavir used as booster
SQV	Saquinavir
TDF	Tenofovir Disoproxil Fumarate

Country Codes	
AL	Algeria
AR	Argentina
AM	Armenia
BR	Brazil
CL	Chile
CN	China
CO	Colombia
DO	Dominican Republic
EG	Egypt
GT	Guatemala
IN	India
ID	Indonesia
KG	Kyrgyzstan
MY	Malaysia
MX	Mexico
MA	Morocco
PA	Panama
PE	Peru
PH	Philippines
RU	Russian Federation
ZA	South Africa
TJ	Tajikistan
TH	Thailand
UA	Ukraine
UY	Uruguay
UZ	Uzbekistan
VN	Vietnam



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ARV Priority List for the Medicines Patent Pool

Working Paper, September 2011

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Background[a]

The Medicines Patent Pool (the "Pool") was established with the support of UNITAID in July 2010 with the aim of enhancing access to affordable HIV medicines in developing countries and promoting the development of adapted formulations, such as paediatric HIV formulations and optimal Fixed Dose Combinations (FDCs). It does so by negotiating voluntary licensing agreements with patent holders (e.g. companies, public research institutions, universities) and in turn licensing out on a non-exclusive basis to entities capable and willing to develop or manufacture products needed to treat HIV in developing countries. The Pool is a mechanism that could facilitate the development of optimal treatment options that could exist if intellectual property on HIV medicines is made available.

Since its inception, the Pool has collaborated with leading experts to identify needed antiretrovirals (ARVs) that should be prioritised for inclusion in the Pool. The first prioritisation was done in October 2009 and elements of it were submitted jointly by UNITAID and the WHO Secretariat to the WHO Expert Committee on the Selection and Use of Essential Medicines[1]. The document submitted to the Committee included lists of needed antiretroviral products and formulations for adults and children, based on the 2006 WHO treatment recommendations for HIV-infected adults, adolescents, infants and children [2, 3]. This document helped to inform the selection of 19 priority ARVs identified in the UNITAID Patent Pool Initiative Implementation Plan of 2009. The 19 priority products, which included a number of pipeline compounds, were: abacavir, atazanavir, cobicistat, darunavir, efavirenz, elvitegravir, emtricitabine, etravirine, fosamprenavir, lamivudine, lopinavir, maraviroc, nevirapine, raltegravir, rilpivirine, ritonavir, saquinavir, tenofovir and vicriviroc.

Since 2009, new clinical evidence has emerged on approved and pipeline products. The WHO issued a revision of the treatment guidelines for infants, children, adults and adolescents in 2010 [4, 5]. Simplified combinations using better-tolerated ARVs are now recommended for 1st and 2nd line therapy. A new therapeutic class was included and third line regimens were considered. In addition, some drugs that were previously recommended are no longer recommended as preferred options, although they remain as alternative treatments in the guidelines.

Promising products have also progressed further in clinical development. New integrase inhibitors, second-generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) and pharmacokinetic enhancers, both as stand-alone drugs and as part of FDCs, are in late stage development and are expected to be approved in their adult formulations shortly.

Finally, the patent status of several key ARVs has changed in many countries since the original list of target compounds was developed, including, for example, the expiry of certain patents.

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[a] The results of an earlier version of this document were presented at the Conference of the International AIDS Society held in Rome in July 20011. In addition, the Medicines Patent Pool would like to thank the following external reviewers for their comments on the draft document: Isabelle Andrieux-Meyer, Pascale Boulet, Pedro Cahn, Alexandra Calmy, Polly Clayden, Carlos Correa, Andy Gray, Mark Harrington, David Hoos, Nagalingeswaran Kumarasamy, Janice Lee, Philippa Musoke, Nelson Otwoma, Carmen Pérez, David Ripin and Marco Vitoria. The Pool remains responsible for the final contents of the document.

In light of these developments, there is a need to update the priority list of ARV candidates for the Medicines Patent Pool.

A first step in updating the priorities for the Pool was the revision of the list of missing formulations that had been submitted to the WHO Expert Committee in 2009. Thus, in February 2011, the Medicines Patent Pool, UNITAID and the WHO HIV/AIDS Department jointly submitted a proposed list of missing drug formulations for adults and children to the WHO Expert Committee based on the new WHO antiretroviral treatment guidelines[b]. The document identified formulations and combinations included in the 2010 WHO treatment guidelines, but were either not available, or there were limited suppliers and access remained a key concern. In addition, the document provided an overview of products in the last phases of development that may be approved before the next meeting of the Committee and may constitute important options for future treatment. The Expert Committee, which met in March 2011, recommended that the list be further prioritised, a process that is being led by the WHO in the context of the Treatment 2.0 initiative [6].

The objective of this working paper is to identify target compounds for the Medicines Patent Pool, based on clinical as well as market and intellectual property (IP) criteria. For the clinical prioritisation, it relies on the work undertaken by the WHO and on published information on the results of clinical trials for pipeline compounds. For the market and IP prioritisation, it is based primarily on the patent information gathered by the Medicines Patent Pool, as well as on other public sources such as the WHO Prequalification website (http://apps.who.int/prequal/), to analyse the market situation around each product.

Methodology

Categories for prioritisation

In order to prioritise among compounds, they were divided into categories depending on whether they have already obtained regulatory approval and their current stage of clinical development.

In Category 1 are compounds that have already received regulatory approval and are available today as single agents and/or in combinations[c].

In Category 2 are pipeline compounds that are in phase III studies and are expected to be available shortly, as single agents and/or in combinations[d].

In Category 3 are pipeline compounds that are in phase II studies as well as promising compounds in phase I.

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[b] Submission endorsed by the following core partners of UNAIDS and WHO's Treatment 2.0 Initiative: Agence Nationale de Recherche sur le SIDA (ANRS), AIDS and Rights Alliance for Southern Africa (ARASA), The Global Fund to Fight AIDS, Tuberculosis and Malaria, HealthGap, International AIDS Society (IAS), International Treatment Preparedness Coalition (ITPC), Médecins Sans Frontières (MSF), Pangaea Global AIDS Foundation, the United States President's Emergency Plan for AIDS Relief (PEPFAR) and the Joint United Nations Programme on HIV/AIDS (UNAIDS).

[c] Category 1 does not include rilpivirine, which recently received FDA regulatory approval in May 2011, but has not yet been reviewed by the WHO in the context of the development of its treatment guidelines.

[d] Category 2 includes rilpivirine, which recently received FDA regulatory approval in May 2011.

Criteria for prioritisation

Compounds in categories 1 and 2 were prioritised based on a set of clinical and market/IP criteria, as described in further detail below. For category 3 (i.e. in early phases of clinical trials), only preliminary information for promising candidates is presented in this analysis and no detailed prioritisation was undertaken at this stage.

Clinical criteria

For category 1 compounds, the Pool based its clinical prioritisation on the 2010 WHO treatment guidelines for adults and children [4, 5]. Products recommended as preferred treatment options in the guidelines for first-line and second-line treatment were considered to be high priority from a clinical perspective; products currently considered for third-line or as alternatives for first and second line were considered to be medium priority[e]; and products not recommended anymore, or not yet included as preferred options in the 2010 guidelines were considered to be low priority.[f]

For category 2 compounds, this document relied on the criteria included in the target product profile used by the WHO at its expert meeting on short-term treatment optimization priorities for antiretroviral drug regimens, which was held in April 2011[7]. These are the following:

- **Safety/Efficacy**: Products must be equivalent or superior to currently available products and require minimal laboratory monitoring.
- **Tolerability:** Products must have minimal side effects and toxicities to improve adherence and reduce treatment failure.
- **Durability:** Products should present a high barrier to resistance and have a long half-life to allow for flexibility in the dosing schedule and minimise the likelihood of resistance developing as a result of missed doses.
- **Stability:** Products should be heat-stable and simple to store over long periods of time with molecular stability.
- **Convenience:** Products should be suitable for once-daily dosing in fixed dose combinations - ideally one pill per day regimens - and simplified paediatric formulations or scored fixed dose combinations - once on one side, twice on the other - with no cumbersome testing requirements and the same dosing schedule for all drugs in a regimen.
- **Special Populations:** Products should be effective in all populations and in conjunction with treatment for other conditions: men and women of all ages, pregnant women, infants and children, people who inject drugs and patients with other co-infections, including tuberculosis, malaria and viral hepatitis.

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[e] This decision was motivated by the fact that the WHO is yet to issue firm recommendations on a third-line regimen for resource-limited settings given the limited evidence currently available to guide third-line strategies [4]. However, as will become apparent when analysing third-line products from a market/IP perspective, widespread IP protection in many LIC and MICs for at least two of the products considered for third-line therapy in the WHO guidelines make them a strong priority for the Pool.

[f] An exception was rilpivirine, which obtained regulatory approval by the FDA in May 2011 and was not available at the time of the latest revision of the guidelines.

The WHO criteria also include cost, highlighting the need for products to be available at the lowest sustainable price[g]. However, many of the key factors influencing cost (e.g. degree of competition in the market, IP protection) were considered by the Pool when evaluating products from a market/IP perspective and were therefore not included in the clinical prioritisation part (see below).

Clinical information on pipeline products is based on clinical trial data on the National Institutes of Health website (www.clinicaltrials.gov) [8] and the EU clinical trials register website (www.clinicaltrialsregister.eu) [9]. In addition, a systematic search of abstracts was conducted from those presented at the XVIII International AIDS Conference (Vienna, July 2010), the 18th Conference on Retroviruses and Opportunistic Infections (Boston, March 2011), the VI IAS Conference on HIV Pathogenesis, Treatment and Prevention (Rome, July 2011) and those published in PubMed [10]. Other references such as the 2011 TAG/i-Base Pipeline Report [11] have also been consulted.

For category 3 compounds, no detailed prioritisation was undertaken, as not enough information is available at this stage to assess the products. However, a general overview of some of the key characteristics of such products has been provided.

Market/IP criteria:

Once compounds had been evaluated according to their clinical significance, category 1 and 2 compounds were separately evaluated according to a set of market/IP criteria in order to determine to what extent patents may act as a barrier to access to different products in developing countries. The following criteria were used to evaluate compounds from a market/IP perspective:

- **Expected Compound Patent Expiry Date:** A medicine may be protected by a number of different patents, relating to the compound, the process to manufacture it, and different forms and formulations of that compound. However, the patent claiming the drug compound or active ingredient is generally considered to be the most relevant one and the most difficult to invent around[h] [12]. The expected expiry date of the compound patent was documented, based on a 20-year term from the filing date of the related international patent application (filed in accordance with the provisions of the Patent Cooperation Treaty or PCT)[i]. Compounds with a longer patent term left were considered to be of higher priority than compounds for which the compound patent has expired or is close to expiry.
- **Compound Patent Status in India:** To the extent that Indian generic manufacturing accounts for more than 80% of annual purchase volumes of antiretrovirals in developing countries [13], compound patent status in India is particularly important in determining IP-related access issues. Thus, the identification of a compound patent or patent application in India was considered to be of higher priority from the market/IP perspective.

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[g] Strategies to achieve this, as per the WHO definition, include negotiations with suppliers, interventions to influence market dynamics, use by countries as appropriate of TRIPS flexibilities and other trade agreements, as well as strategies that might include appropriate dose reduction and improvements in manufacturing and delivery processes.

[h] In addition to patents, data exclusivity protection in certain countries may also be a barrier to market competition in certain jurisdictions. While this document does not assess data exclusivity issues, the Medicines Patent Pool does ensure that data exclusivity is waived by patent holders that license to the Pool.

[i] Actual expiry date may differ from country to country in accordance with national patent laws.

- **Compound Patent Status in Other Countries:** In addition to India, the extent to which the compound patents were in force in other low- and middle-income countries, including other countries of manufacture of generic ARVs, was evaluated based on available data. Illustrative examples of countries where compound patents were either granted or pending, as well as those designated in the international application filed under the PCT have been included in Table 2 and 4, below. The information provides a snapshot at a particular point in time based on the information that was available to the Medicines Patent Pool.
- **Other Relevant Patents (with expiry dates):** In addition to compound patents, patents may exist on specific forms of the compound (e.g. hydrate form of the drug salt), formulations, combinations, new indications and/or the manufacturing process for the drug. Such patents may represent less of a barrier to generic competition because generic companies can often develop non-infringing ways to make the same drug or successfully challenge the validity of such patents[j] [14]. Such "secondary patents" may also not be patentable in some jurisdictions. Nevertheless, in some cases they may represent an obstacle to the development of a generic version of specific formulations. As such, other important patents relevant to the drug have been noted where such information was available, along with their expected expiry date, based on a 20-year term from the filing date of the related international patent application.
- **Geographical Coverage of Other Relevant Patents:** Similar to compound patent status in other countries, the geographical coverage of other patents relevant to the manufacturing of a drug was evaluated for the low- and middle-income countries (LICs and MICs) for which information was available.
- **Current Licences:** Even where a patent exists in a particular jurisdiction, generic supply may be possible where licences to use the relevant patents exist. This can happen either through government issued compulsory licences, or through voluntary licences[15]. In order to fully understand the access situation with respect to specific ARVs, voluntary and compulsory licences, non-assert declarations, and immunity-from-suit agreements were analysed to the extent that information about the terms and conditions of the agreements were publicly available. While such licences may allow lower-cost generic drugs to be made and sold, there are often several restrictions included in voluntary agreements. To the extent that such information was publicly available, they have been noted in Tables 2 and 4.
- **Number of WHO Prequalified or FDA Approved Generics:** The number of WHO prequalified or FDA tentatively generic suppliers making the compound or making it in combination with other products, has been noted as a proxy for the extent to which there is generic competition in the market. This information was obtained from the website of the WHO Prequalification Programme [16].

Information on patents status has been obtained from the Patent Status Database for Selected HIV Medicines, a resource publicly available on the Medicines Patent Pool website [17]. The database provides information on the patent status of selected ARVs in a large number of low- and middle-income countries. The data was obtained from and cross-checked between a variety of sources, including many local patent offices that agreed to make this information available via collaboration with the World Intellectual Property Organization (WIPO). Wherever patent information was not available from the database

[j] Even where some secondary patents are vulnerable to challenge, however, the legal process to invalidate them are often long and costly. The European Commission, for instance, estimates that it takes an average of almost three years for invalidation proceedings to be completed. During the pendency of such proceedings, interim injunctive measures may prevent the entry of a generic alternative.

(e.g. for enfuvirtide, nelfinavir and tipranavir), this document relies on the limited information gathered from other sources, in particular, MSF's publication *Untangling the Web of Antiretroviral Price Reductions* (2011) [18].

Summary of Results

Category 1 –Compounds with Regulatory Approval

Clinical and market/IP priorities of Category 1 compounds are presented in Tables 1 and 2 respectively. Clinical prioritisation for compounds in Category 1 is based on their position within the 2010 WHO Treatment guidelines (i.e. included or not, first-line, second-line, or third-line), as well as the extent to which formulations containing the compound have been included in the Updated List of Missing Drug Formulations for HIV Treatment presented to the 18th Expert Committee on the Selection and use of Essential Medicines. Formulations identified in the WHO Meeting Report on Short-Term Priorities for Antiretroviral Drug Optimization of April 201 [7] are listed in bold.

Table 1: Clinical Prioritisation of Category 1 Compounds

Compound	WHO Guidelines		Missing Drug Formulation for HIV Treatment[k]		Clinical Priority
	Adult	Paediatric	Adult	Paediatric	
Abacavir (ABC)		Recommended for first- and second-line as alternative regimen	-	•ABC/3TC •ABC/3TC/NVP •ABC/3TC+EFV •ABC/3TC+LPV/r	**Medium** (paediatrics)
Atazanavir (ATV)	Recommended for second-line (preferred option)		•**ATV/r** •TDF/3TC/ATV/r	•ATV/r	**High** (priority for second line)
Darunavir (DRV)[l]	Tentative recommendation for third-line		•DRV/r •TDF/3TC+DRV/r •ETV+DRV/r •DRV/r+RAL •DRV/r+ETV+RAL	•DRV/r	**Medium** (priority for third line)
Didanosine (ddI)		Restricted to second line and preferably replaced by 3TC.	-	-	**Low** (no longer preferred option, but still used for children)
Efavirenz (EFV)	Recommended for first-line (preferred option)	Recommended for first-line for children > 3 years	•**TDF/3TC/EFV**	•ABC/3TC+EFV	**High** (priority for first line)
Emtricitabine (FTC)	Recommended for first- and second line (considered interchangeable with 3TC)		•TDF/FTC+NVP •TDF/FTC/EFV •TDF/FTC/ATV/r •TDF/FTC+LPV/r •TDF/FTC+DRV/r •AZT/FTC+LPV/r •AZT/FTC+ATV/r	•TDF/FTC	**High** (considered as interchangeable with 3TC).

[k] The missing drugs and formulations for HIV treatment is based on the 'Updated List of Missing Drug Formulations for HIV Treatment to be Reviewed by the WHO 18th Expert Committee on the Selection and Use of Essential Medicines' (February 2011) and has been updated to take into account further expert opinions. Therefore, some combinations have been added and others removed. In some cases, the formulations have been developed but are produced by few manufacturers and access problems remain. Those cases have also been included in the table. Some combinations may be difficult to co-formulate due to, for example, the pill size or different dosing schedules. In these situations a co-blister pack would be desirable. For details on the priorities for optimization of adult and paediatric treatment, see WHO report at: http://www.who.int/hiv/pub/arv/short_term_priorities/en/index.html

[l] Darunavir (DRV) has the potential to be used in 2nd line, but is currently only recommended by WHO for use in 3rd line.

Compound	WHO Guidelines		Missing Drug Formulation for HIV Treatment[l]		Clinical Priority
	Adult	Paediatric	Adult	Paediatric	
Enfuvirtide (T-20)	-	-	-	-	**Low** (not recommended by WHO)
Etravirine (ETV)	Tentative recommendation for third-line	-	•ETV+DRV/r	•ETV	**Medium** (priority for third line)
Fosamprenavir (FPV)	-	-	-	-	**Low** (not recommended by WHO)
Indinavir (IDV)	-	-	-	-	**Low** (not recommended by WHO)
Lamivudine (3TC)	Recommended for first- and second-line	Recommended for first- and second-line	•**TDF/3TC/EFV** •TDF/3TC+NVP •TDF/3TC/ATV/r •TDF/3TC+LPV/r •TDF/3TC+DRV/r •AZT/3TC+LPV/r •AZT/3TC+ATV/r	•ABC/3TC •TDF/3TC •ABC/3TC/NVP •ABC/3TC+EFV •**AZT/3TC+LPV/r** •ABC/3TC+LPV/r •**TDF/3TC+NVP** •**TDF/3TC+LPV/r** •**TDF/3TC+DRV/r**	**High** (priority for first- and second-line)
Lopinavir (LPV)	Recommended for second-line (preferred option)	Recommended for first- line below 24 months if prior exposure to NVP, and second-line	•LPV/r •TDF/3TC+LPV/r •AZT/3TC+LPV/r •3TC/LPV/r	•**LPV/r** •**AZT/3TC+LPV/r** •ABC/3TC+LPV/r	**High** (priority for first- and second-line)
Maraviroc (MVC)	-	-	-	-	**Low** (not recommended by WHO)
Nelfinavir (NFV)	-	-	-	-	**Low** (not recommended by WHO)
Nevirapine (NVP)[m]	Recommended for PMTCT and alternative to EFV in first-line	Recommended for first-line (if no prior exposure to NVP)	•**TDF/3TC+NVP**	•NVP •ABC/3TC/NVP	**High** (priority for PMTCT and for children)
Raltegravir (RAL)[n]	Tentative recommendation for third-line[19]	-	•ETV+RAL •DRV/r+RAL	•RAL	**Medium** (priority for third-line)

[m] Nevirapine (NVP) extended release was approved by US FDA in March 2011.

[n] Raltegravir can also be used in treatment naïve patients and does not need a booster. However, is currently recommended by WHO for use in third line only.

Compound	WHO Guidelines		Missing Drug Formulation for HIV Treatment*		Clinical Priority
	Adult	Paediatric	Adult	Paediatric	
Ritonavir (r)	Recommended for second- and third-line (as pharmacological booster)	Recommended for first-line (as pharmacological booster) in children below 24 months with prior exposure to NVP	•r(heat stable tablet) •ATV/r •DRV/r •LPR/r •TDF/3TC/ATV/r •TDF/3TC+LPV/r •TDF/3TC+DRV/r •AZT/3TC+LPV/r •AZT/3TC+ATV/r •ETV+DRV/r •DRV/r+RAL	•**r(heat stable tablet, sprinkle)** •LPV/r •ATV/r •DRV/r •**AZT/3TC+LPV/r** •ABC/3TC+**LPV/r**	**High** (priority for second-, and third-line for adults and first-line for children)
Saquinavir (SQV)	No longer a preferred protease inhibitor in WHO guidelines (except when TB co-infection if rifabutin not available)	-	-	-	**Low** (not recommended by WHO except for TB co-infection if rifabutin not available)
Stavudine (d4T)	No longer recommended	Recommended as alternative to AZT and ABC for first-line	-	-	**Medium** (recommended as alternative for children, no longer recommended for adults)
Tenofovir (TDF)	Recommended for first- or second-line (if not used in first line)	Key WHO research priority for first-line	•**TDF/3TC+NVP** •**TDF/3TC/EFV** •TDF/3TC/ATV/r •TDF/3TC+LPV/r •TDF/3TC+DRV/r	•**TDF/3TC**° •**TDF/3TC**+NVP •**TDF/3TC+LPV/r** •**TDF/3TC**+DRV/r	**High** (priority for first-line)
Zidovudine (AZT)	Recommended for first- or second-line (if TDF-based first line)	Recommended for first-line (preferred)	•AZT/3TC+LPV/r •AZT/3TC+ATV/r •AZT/3TC+DRV/r	•AZT •**AZT/3TC+LPV/r**	**High** (priority for first- and second-line)

° Scored adult-strength dissolvable (soluble or dispersible) formulation of TDF/3TC would become a priority for paediatrics first-line only if TDF is approved for use in younger children and appropriate dosing is established.

Table 2: Market/IP Prioritisation of Category 1 Compounds

Compound	Expected Compound Patent Expiry Date	Compound Patent Status in India	Compound Patent Status in Other Countries	Other Relevant Patents (expiry date)	Geographical Coverage of Relevant Patents	Current Voluntary Licences[p]	Number of WHO Prequalied or FDA Approved Generics	Market/IP Priority
Abacavir (ABC)	Expired in June/Dec. 2010	No	Probably expired in most jurisdictions in which it was originally granted	New intermediates (2015); Hemisulfate salt (2018); Oral solution for paediatric use (2019)	Granted or pending in several LIC/MICs. Paediatric solution granted in India and other LIC/MICs	Yes, several licensees, but possible restrictions and limited geographical scope (69 countries)	5 or more for adult formulations but three approved for paediatric formulations	**Medium** (many suppliers; compound patent expired, but paediatric formulation and salt patent can be a barrier in some jurisdictions)
Atazanavir (ATV)	2017	Initial application withdrawn but divisional application pending	Granted or pending in several LIC/MICs, including e.g. AR, BR, CN, KG, MY, PH, TJ, TH	Bisulfate salt (2018); Use in HIV Therapy (2012); Process (2025)	Granted or pending in several LIC/MICs.	Yes, limited number of licensees, possible restrictions and limited geographical scope (SSA and India; 49 countries)	Two	**High** (few suppliers; compound patent pending in India and granted in other countries)

[p] With the exception of the licences obtained by the Medicines Patent Pool, which are public, detailed terms and conditions of the other voluntary licence agreements are confidential and it is not possible to undertake a thorough analysis to identify the extent to which certain restrictive conditions have been included. Restrictions included in certain voluntary licences include, for example, restrictions on the manufacturing of active pharmaceutical ingredients (API), restrictions on the development of fixed-dose combinations, restrictions on the ability to supply countries issuing compulsory licences, lack of unilateral termination clauses for licensees, prohibition to challenge patents, limited geographical scope, etc.

Compound	Expected Compound Patent Expiry Date	Compound Patent Status in India	Compound Patent Status in Other Countries	Other Relevant Patents (expiry date)	Geographical Coverage of Relevant Patents	Current Voluntary Licences[1]	Number of WHO Prequalied or FDA Approved Generics	Market/IP Priority
Darunavir (DRV)	Aug. 2013	No	No	Specific (2016); Method of Use (2019); Comb. w/ RTV (2022); Pseudopolymorph (2023); Prep. of key intermediates (2025); Comb. w/ RTV & TDF (2025)	Granted or pending in several LIC/MICs	Yes, but only for packaging and distribution; limited number of licensees and limited geographical scope (SSA, LDCs and India)	None	**Medium** (no compound patents in LIC/MICs for which information is available, several other patents pending/granted in many countries, but no generics currently on the market)
Didanosine (ddI)	Expired in 2006	No	No	Improved oral formulation (July 2012) Enteric-coated (2018)	Granted or pending in several LIC/MICs	Yes, several licensees, but possible restrictions and limited geographical scope	Three	**Medium** (compound patent expired but patent on enteric-coated formulation may act as barrier)
Efavirenz (EFV)	Aug. 2013	No	Granted or pending in some LIC/MICs, including e.g. AR, BR*, CL, CN, MX, RU, ZA, TH*, UA	Comb. w/ LPV, FTC, EFV (2024) Comb w/ EFV + FTC (2026)	Granted or pending in several LIC/MICs	Yes, few licensees, possible restrictions and very limited geographical scope (South Africa and 10 countries in SSA).	5 or more	**Medium** (no compound patent in India, many suppliers, but still compound patents in other LIC/MICs and combination patents with TDF and FTC)

Compound	Expected Compound Patent Expiry Date	Compound Patent Status in India	Compound Patent Status in Other Countries	Other Relevant Patents (expiry date)	Geographical Coverage of Relevant Patents	Current Voluntary Licences[p]	Number of WHO Prequalied or FDA Approved Generics	Market/IP Priority
Emtricitabine (FTC)	Expired in 2010	No	Originally granted in several LIC/MICs, (including e.g. CN, MY, OAPI, PH, RU and ZA) but probably expired or due to expire shortly	No[q]	No	Yes, immunity from suits issued in context of TDF licence (112 countries)	Two	**Low** (compound patent expired)
Enfuvirtide (T-20)	2014	No	Unknown	Method for synthesising enfuvirtide (2019)	Granted in CN. Limited information in other countries.	No	None	**Low** (based on currently available information)
Etravirine (ETV)	2019	Granted	Granted or pending in several LIC/MICs, including e.g. ARIPO, AM, AR, BR, CL, CN, EAPO, ID, KG, MY, MX, OAPI, PH, RU, ZA, TJ, UA, VN	Novel series (2026) New forms (2026)	Granted or pending in several LIC/MICs	Only for packaging and distribution; limited number of companies and limited geographical scope (SSA)	None	**High** (no generic suppliers; compound patent granted in India and other countries)
Fosamprenavir (FPV)	2018	Pending	Granted or pending in several LIC/MICs, including e.g. ARIPO, AM, AR, CL, CN, CO, EAPO, ID, KG, MY, MX, OAPI, PE, PH, RU, ZA, TJ, TH, UA	Calcium salt (2019)	Granted or pending in several LIC/MICs	Yes, several licensees, but possible restrictions and limited geographical scope (69 countries)	None	**High** (no generic suppliers; compound patent pending in India and granted in other countries)
Indinavir (IDV)	Nov. 2012	No	Granted or pending in some LIC/MICs, including e.g. RU, ZA, UA	-	NA	None	Two	**Low** (limited patent issues and due to expire shortly)

[q] Information based on the Medicines Patent Pool patent status database. However, a list of other patents relating to FTC included as annex to licence between Medicines Patent Pool and Gilead Sciences.

Compound	Expected Compound Patent Expiry Date	Compound Patent Status in India	Compound Patent Status in Other Countries	Other Relevant Patents (expiry date)	Geographical Coverage of Relevant Patents	Current Voluntary Licences*	Number of WHO Prequalied or FDA Approved Generics	Market/IP Priority
Lamivudine (3TC)	Expired in Feb. 2010	No	Originally granted in several LIC/MICs, including e.g. MY, PH, RU, ZA but probably expired or due to expire shortly	Crystal form (June 2012) New formulation (2018)	Granted or pending in several LIC/MICs	Yes, several licensees, but possible restrictions and limited geographical scope (69 countries)	5 or more	**Low** (compound patent expired, many suppliers, but other form and formulation patents may be an issue)
Lopinavir (LPV)	2016	No	Granted or pending in several LIC/MICs, including e.g. AR, BR, CN, CO, MX, PH, ZA, TH	LPV/r Soft-gel caps (2017) LPV/r tablet formulation (2026) LPV/r tablet formulation (2024)	Granted or pending in several LIC/MICs	None	Three	**High** (few suppliers; compound patent in several countries; formulation and combination patents pending or granted in several LIC/MICs; no voluntary licenses)
Maraviroc (MVC)	2019	Granted	Granted or pending in several LIC/MICs, including e.g. AL, ARIPO, AM, AR, BR, CL, EAPO, EG, GT, ID, KG, MY, MX, MA, OAPI, PA, PE, PH, RU, ZA, TJ, UA, UY, UZ, VN	Crystal form (2021)	Granted or pending in several LIC/MICs	None	None	**High** (no generic suppliers; compound patent granted in India and other countries)
Nelfinavir (NFV)	2014	No	Not known	Not known	-	-	One	**Low** (based on currently available information)

Compound	Expected Compound Patent Expiry Date	Compound Patent Status in India	Compound Patent Status in Other Countries	Other Relevant Patents (expiry date)	Geographical Coverage of Relevant Patents	Current Voluntary Licences[r]	Number of WHO Prequalied or FDA Approved Generics	Market/IP Priority
Nevirapine (NVP)	Expired in Nov. 2010	No	Granted or pending in several LIC/MICs, including e.g. OAPI, PH, RU, ZA	Hemihydrate formulation (2018) Extended release formulation (2028)	Granted or pending in several LIC/MICs	Yes, BI has policy of non-assert declarations, but potential restrictions for manufacturing in countries with patents and limited geographical scope (78 countries)	5 or more	**Low** (compound patent expired[r] but formulation patents may be an issue, e.g. for new extended release formulation)
Raltegravir (RAL)	2022	Granted	Granted or pending in several LIC/MICs, including e.g. BR, CL, CN, CO, MX, PH, ZA, UA, UZ, VN	Potassium salt (2025)	Granted or pending in several LIC/MICs	Yes, only two licensees. Also, possible restrictions and limited geographical scope (SSAs and LICs)	None	**High** (compound patent granted in India and other LIC/ MICs)

[r] Situation may need to be reassessed if the patent on extended release NVP is granted in LICs or MICs, and the patent acts as a barrier to the sale of the extended release formulation

Compound	Expected Compound Patent Expiry Date	Compound Patent Status in India	Compound Patent Status in Other Countries	Other Relevant Patents (expiry date)	Geographical Coverage of Relevant Patents	Current Voluntary Licences*	Number of WHO Prequalied or FDA Approved Generics	Market/IP Priority
Ritonavir (RTV)	Dec. 2013/2014	No	Granted in few LIC/MICs, including e.g. MX, PH	Crystalline polymorph (2019) LPV/r tablet formulation (2026) LPV/r tablet formulation (2024)	Granted or pending in several LIC/ MICs; opposed in India	None	One	**High** (few suppliers; no compound patent in India but in force in some LIC/MICs, formulation and combination patents pending in India and granted in other countries); no substitute boosters; needed to boost other PIs
Saquinavir (SQV)	Expired in Dec. 2010	Expired	Originally granted in many LIC/MICs, expired in many countries, but patent still in force in a few jurisdictions	Improved composition (2016) Oral dosage form (2024)	Granted or pending in several LIC/ MICs	Several licences and technology transfer agreements signed	None	**Medium** (compound patent expired in many but not all jurisdictions)
Stavudine (d4T)	Expired in Dec. 2007	No	No	None have been identified	-	Yes, several licensees. Commitment not to enforce its patents in SSA since 2001.	5 or more	**Low** (Many suppliers; compound patent expired; other relevant patents have not been identified at this stage)

Compound	Expected Compound Patent Expiry Date	Compound Patent Status in India	Compound Patent Status in Other Countries	Other Relevant Patents (expiry date)	Geographical Coverage of Relevant Patents	Current Voluntary Licences[5]	Number of WHO Prequalied or FDA Approved Generics	Market/IP Priority
Tenofovir (TDF)	Expired	No	No	Fumarate salt (2018) Ester prodrug (2017) Comb. w/ LPV, FTC, EFV (2024) Comb w/ EFV + FTC (2026)	Granted or pending in several LIC/MICs	Yes, several licensees but possible restrictions and limited geographical scope[5]	5 or more	**Medium** (many suppliers; patents on the fumarate salt in some LIC/MICs, process patents in India and combination patents in many LIC/ MICs)
Tipranavir (TPV)	2015	No	Patents appear to have been filed in some developing countries but detailed information not avaiable [18]	Not known	Not known	None	None	**Low** (limited patent information available)
Zidovudine (AZT)	Expired in 2006	No	No	AZT/3TC tablet formulation (2017)	Granted in many developing countries	Yes, several, but limited geographical scope (69 countries)	5 or more	**Low** (many suppliers; compound patent expired; patents on combinations)

[5] On July 12, 2011, Gilead Sciences granted a licence covering tenofovir to the Medicines Patent Pool. While certain restrictions remain, the geographical scope was expanded to 112 countries. Details and the text of the licence available at www.medicinespatentpool.org

Category 2

Category 2 presents compounds that are close to regulatory approval (cobicistat, dolutegravir and elvitegravir) or have recently received approval (rilpivirine) (Table 3 and 4). Several promising combinations that include these compounds and are under development have also been noted.

Table 3: Clinical Prioritisation of Category 2 Compounds

Compound	Therapeutic Class	Combinations	Safety / Efficacy	Tolerability	Durability	Stability	Convenience	Special pop'ns	Cost	Clinical Priority[1]
Cobicistat (COB)	Pharmaco-kinetic booster	Already in phase III (study 236-0102) together with TDF/FTC[2] and ELVITEGRAVIR (in co-formulation) vs TDF/FTC/EFV. No results published yet but announced by Gilead on August 15th to be as effective as Atripla [20] An agreement to develop DRV/COB FDC announced in July 2011 [21]	Phase II study 236-0105 comparing cobicistat and ritonavir showed similar efficacy in both groups [22]	In phase II study 236-0102, cobicistat showed reduction of estimated glomerular filtration rate. Data at 24 weeks show no significant renal toxicity compared with ritonavir (study NCT01363011 [22])	No antiviral activity, so it does not induce resistances.	Does not need refrigeration	One pill once daily	PAED: No clinical trials in children yet. TB: Cobicistat inhibits CYP450 [23], so may need dose adjustments with rifampicin or use with rifabutin. Not yet approved for use in pregnant women and no ongoing studies.	May not be developed as stand-alone drug	**High** (promising compound; further clinical information required for more in-depth assessment)

[1] The level of priority of pipeline compounds will be re-considered once further clinical evidence is available and regulatory approval is obtained.

Compound	Therapeutic Class	Combinations	Safety / Efficacy	Tolerability	Durability	Stability	Convenience	Special pop'ns	Cost	Clinical Priority
Dolutegravir (DLG)	Integrase inhibitor	ABC/3TC/DLG entered phase III trial comparing with TDF/FTC/EFV [24]	Results of phase IIb study on naïve treatment patients (SPRING-1) showed rapid viral load reductions [25, 26]. 50mg dose BID is effective in treatment experienced patients with mild and heavy integrase resistance [27]. A phase III trial with twice daily dose in treatment experienced and naïve patients has already started[8])	SPRING-1 study results on naïve treatment patients presented showed less drug-related adverse events in DLG group compared with EFV (6% vs. 18%), and no serious adverse event was considered related to DLG [24-26] Recent results at 96 weeks confirm only 17% patients (n=24) presented grade 3 adverse events. No grade 4 events were observed [27]	Integrase inhibitor class does not have lower genetic barrier to resistance than EFV [28] but no comparison with boosted PIs Preliminary results on SPING-1 trial presented in Vienna showed that only 1 patient in the DLG group (n=155) experienced virologic failure.	Does not need refrigeration	Can be used as one pill once daily	PAED: Phase II trial ongoing, but not enough data yet [8] TB: No information yet, although other integrase inhibitors are not TB friendly (RAL) Studies ongoing with pregnant women.	Eligible for dose/cost reduction	**High** (promising compound; further clinical information required for more in-depth assessment)

Compound	Therapeutic Class	Combinations	Safety / Efficacy	Tolerability	Durability	Stability	Convenience	Special pop'ns	Cost	Clinical Priority[1]
Elvitegravir (EVG)	Integrase inhibitor	Already in phase III (study 236-0102) together with TDF/FTC[2] and COB vs. TDF/FTC/EFV. No results published yet but announced by Gilead on August 15th to be as effective as TDF/3TC/EFV[29]	In phase II 236-0102 study comparing EVG in combination with TDF/FTC/COB vs. TDF/FTC/EFV 90% vs. 83% had <50 copies/ml at 24 weeks and 48 weeks [22] Recent results show non-inferiority vs raltegravir at 48 weeks [30]	In phase II study 236-0102 study showed less efavirenz-related side effects. ("lower rate of drug-related central nervous system (17%) and psychiatric (10%) adverse events versus EFV/FTC/TDF (26 and 44%, respectively) [22]	Integrase inhibitor class does not have lower genetic barrier to resistance than EFV [28] but no comparison with boosted PIs	Does not need refrigeration	One pill once daily (only if boosted)	PAED: A phase II study for children over 12 years. No study yet for under 12. TB: Drug interactions with rifampicin (contraindicated)[31], needs to be used with rifabutin. Not yet approved for use in pregnant women and no ongoing studies.	Low dose of EVG would reduce cost (now dosed at 150 mg)	**High** (promising compound; further clinical information required for more in-depth assessment)

Compound	Therapeutic Class	Combinations	Safety / Efficacy	Tolerability	Durability	Stability	Convenience	Special pop'ns	Cost	Clinical Priority*
Rilpivirine[u] (RIL)	NNRTI	TDF/3TC/RIL has been approved by FDA for use in first line. TDF/FTC/RIL has already been studied vs. TDF/FTC/EFV [32].Another possible combination would be using 3TC instead of FTC. 3TC is cheaper and eligible for dose reductions.	RIL vs. EFV comparative studies showed non-inferiority in the proportion of patients that reached undetectable viral load in both groups at 48 weeks (84.3% vs. 82.3%) (pooled results of studies THRIVE and ECHO [32]) But RIL probably not suitable for patients with high viral loads.	Improved tolerability profile compared with EFV (at 96 weeks, RIL group showed reduced rash, less sleep disturbance and lower CNS toxicity compared with EFV, being serious adverse events similar in both groups as reported in TMC278-C204 study [33]	Pre-clinical and phase I studies support long acting injectable formulation [34]. Higher virological failure was found in the RIL group (9% vs. 4.8%) (pooled results of studies THRIVE and ECHO EFV [32])	Does not need refrigeration	One pill once daily (potential for long acting injectable formulation)	PAED: Still in phase II studies (NCT00799864 trial) but only in adolescents. TB: drug interactions with rifampicin. Thus use of rifabutin Not yet approved for use in pregnant women and no ongoing studies.	Potentially low price due to low dose used.	**High** (promising compound, yet to be assessed by the WHO ART Guidelines Committee)

Table 4: Market/IP Prioritisation of Category 2 Compounds

Compound	Expected Compound Patent Expiry Date	Compound Patent Status in India	Compound Patent Status in Other Countries	Other Relevant Patents (expiry date)	Geographical Coverage of Relevant Patents	Current Voluntary Licences	Number of WHO Prequalified or FDA Approved Generics	Market/IP Priority

[u]Rilpivirine (RIL) and TDF/3TC/RIL obtained regulatory approval from the US FDA in May and August 2011 respectively, but were not available at the time of the latest revision of the WHO guidelines, which is why it has been included in Category 2. Level of priority of rilpivirine will be re-assessed once it is considered by the WHO ART Guidelines Committee.

Cobicistat (COB)	2028	Pending	Pending in several LIC/MICs, including e.g. AL, ARIPO, AM, AR, BR, CN, EAPO, EG, ID, KG, MX, MA, OAPI, RU, ZA, TJ, VN	None have been identified at this stage	NA	Yes[v]	NA	**High** (compound patent pending in India and other countries; would be potential substitute for ritonavir)
Dolutegravir (DLG)	2026	Pending	Granted or pending in several LIC/MICs, including e.g. AM, CN, EAPO, KG, MX, PH, RU, ZA, TJ, UZ	Synthesis processes (2029) Intermediates (2029)	Granted or pending in several LIC/MICs, including India	No	NA	**High** (compound patent pending in India and other countries; potential for very low production costs)
Elvitegravir (EVG)	2023	Pending	Granted or pending in several LIC/MICs, including e.g. AR, BR, CL, CN, Colombia, MY, MX, PE, PH, RU, ZA, VN	Crystal form (2025) Improved pharmacokinetics w/ RTV (2026)	Granted or pending in several LIC/MICs, including India	Yes[w]	NA	**High** (compound patent pending in India and other countries)
Rilpivirine (RIL)	2022	Granted	Granted or pending in several LIC/MICs, including e.g. AR, ARIPO, BR, CL, CN, EG, Jordan, MY, MX, OAPI, PA, PH, ZA, UA, VN	None have been identified at this stage	NA	Yes, voluntary licences with 3 companies but possible restrictions and limited geographical scope.	NA	**High** (compound patent granted in India and granted or pending in other countries; potential for very low production costs)

[v] On July 12, 2011, Gilead Sciences granted a licence covering cobicistat to the Medicines Patent Pool. While the licence includes certain restrictions, the geographical scope is 103 countries. Details and the text of the licence available at www.medicinespatentpool.org

[w] On July 12, 2011, Gilead Sciences granted a licence covering elvitegravir to the Medicines Patent Pool. While the licence includes certain restrictions, the geographical scope is 100 countries. Details and the text of the licence available at www.medicinespatentpool.org

Category 3

In category 3 (Table 5) presents promising compounds that have entered phase II of development. Additionally, some compounds in phase I showing promising results have been included.

Table 5: Clinical Review of Category 3 Compounds*

Adult	Therapeutic class	Development study phase	Comments
APRICITABINE	NRTI	Phase II	Development resumed recently. No data yet.
BMS-663068	Attachment inhibitor	Phase II	New therapeutic class
CENICRIVIROC	CCR5 inhibitor	Phase II	Recently entered phase II (study NCT01338883) [8]
CMX-157	NRTI	Phase II	Recently entered phase II [11]
CTP-518	PI	Phase I/II	Slow hepatic elimination (long half-life)
DAPIVIRINE	Vaginal microbicide	Phase I/II/III	Long-lasting properties.
ELVUCITABINE	NRTI	Phase II completed, but development interrupted	Potential to be QD, weekly, monthly. Potentially low price, but concerns with clinical trial results
FESTINAVIR	NRTI	Phase II [35]	Similar to d4T but less toxic. Long-acting properties
FOZIVUDINE	NRTI	Finished phase II but development interrupted	Lipid conjugate of AZT that reduces toxicity and increases activity [36]
GS-7430	NRTI	Phase I	Oral pro-drug of TDF with potential to improve efficacy and safety compared with TDF[37].
GSK-744	Integrase inhibitor	Phase II	Phase II study showed safety and efficacy [9] A phase I study investigates its use as long-acting IV or IM injection [9]
GSK-761	NNRTI	Phase II	Development on hold due to toxicity issues [11].
IBALUZIMAB	CD4 monoclonal antibody	Phase II	New therapeutic class, interesting as long acting life and potential weekly administration
LERSIVIRINE	NNRTI	Phase II	Phase II results presented in July 2011: once daily showed similar efficacy to efavirenz over 48 weeks in treatment-naïve patients. [38]
PPL-100	PI	Phase I	High resistance barrier and easy to co-formulate.
PRO-140	Monoclonal CCR5 antibody	Already entered phase II (NCT01272258 trial[39])	Long-acting properties
RACIVIR	NRTI	Phase I	Once daily, can be used in experienced patients.
SPI-452	Pharmacokinetic enhancer	Phase I	Together with COB, only booster in advanced development
TENOFOVIR vaginal gel	NRTI	Phase II	It has shown effective reduction of HIV acquisition (CAPRISA 004 study [40])

* Products included in this table are in early stage of development and may not reach approval. The list is not exhaustive. A full analysis, including indication of level of priority from a clinical and market/IP perspective, will be undertaken once products enter Phase III.

Conclusions

By considering both the clinical and market/IP criteria, priority ARV compounds for the Medicines Patent Pool have been identified. Compounds that were considered medium or high priority according to both sets of criteria are Level 1 priorities for the Pool. These are compounds that are either recommended by the WHO or appear to be very promising and for which there are patents that could act as barriers to generic competition. Compounds that were considered to be medium or high priority from a clinical perspective (i.e. medically important in light of WHO's current guidelines) but low from an IP perspective (i.e. limited patent barriers) are Level 2 priorities. Finally, compounds that were considered low from a clinical perspective, but were high or medium from a market/IP perspective were considered Level 3 priorities. The latter are compounds for which patent barriers are present, and while not recommended as preferred treatment options today, are still being used or have the potential of being used or being recommended in certain situations.

The list of priority compounds below will replace the earlier list of 19 products as the priority targets for inclusion in the Medicines Patent Pool. The list will be periodically updated, as new clinical or patent information on the different compounds becomes available, WHO treatment guidelines are revised or the patent status of compounds changes.

Table 6: Summary of Priorities for the Medicines Patent Pool

Compound	Clinical Priority	Market/IP Priority
Level 1 Priorities (medium or high priority under both criteria)		
Atazanavir (ATV)	High	High
Dolutegravir (DLG)*	High	High
Cobicistat (COB)*	High	High
Elvitegravir (EVG)*	High	High
Lopinavir (LPV)	High	High
Rilpivirine (RIL)	High	High
Ritonavir (r)	High	High
Efavirenz (EFV)	High	Medium
Tenofovir (TDF)	High	Medium
Etravirine (ETV)	Medium	High
Raltegravir (RAL)	Medium	High
Abacavir (ABC)	Medium	Medium
Darunavir (DRV)	Medium	Medium
Level 2 Priorities (medium or high for clinical and low for market/IP)		
Lamivudine (3TC)	High	Low
Nevirapine (NVP)	High	Low
Zidovudine (AZT or ZDV)	High	Low
Emtricitabine (FTC)	High	Low
Stavudine (d4T)	Medium	Low

Level 3 Priorities (medium or high for market/IP and low for clinical)		
Fosamprenavir (FPV)	Low	High
Maraviroc (MVC)	Low	High
Didanosine (ddI)	Low	Medium
Saquinavir (SQV)	Low	Medium

(*) Compounds in late stages of clinical trials (Phase III studies).

Products considered to be a low priority under both sets of criteria are considered not to be a priority for the Medicines Patent Pool.

Table 7: Compounds not considered to be a priority for the Pool at this stage

Compound	Clinical Priority	Market/IP Priority
Not Priorities		
Enfuvirtide (T-20)*	Low	Low
Indinavir (IDV)	Low	Low
Nelfinavir (NFV)*	Low	Low
Tipranavir (TPV)*	Low	Low

* Very limited patent information was available on these compounds, and could become Level 3 priority if additional patent information indicated that patent barriers are greater than currently known

Compounds in phase II have not been included in the list of priorities provided, as not enough information is available. As compounds move to phase III, and further clinical information becomes available, the Pool will assess those compounds according to the same criteria as the others.

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